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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/044,569	01/11/2002	Jean-Marie R. Saint-Remy	920522-905380	9454

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/044,569	SAINT-REMY ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *2-4 and 13-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-12 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/17/03 &4/16/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-21 are pending.

2. Applicant's election with traverse of Group IV, claims 1, 5-12 and 21 drawn to a method for preventing and/or treating the systemic inflammatory response syndrome with a partial inhibitor of factor VIII, wherein the partial inhibitor is an antibody and the antibody that is produce by KRIX 1as the species (the species corresponding to claim 5) as the filed on 2/02/04, is acknowledged.

Upon reconsideration, the Examiner extended the search to cover anti-fVIII C1 domain antibody.

Applicant's traversal is on the grounds that systemic inflammation is a characteristic common to all of the diseases cited in claim 1, providing a common etiological platform for a meaningful therapeutic approach. Applicant submits that this systemic inflammation can be treated and prevented according to the present invention by partial inhibition of Factor VIII. Moreover, it is believed that the method of claim 1 relates to the same inventive concept as the claim relating to a pharmaceutical composition in claim 13 (and thus should be entitled to the same scope) so that in fact alleged inventions of Group VII and VIII should be considered as unitary with claim 1. This is not found persuasive because the pathological conditions differ in etiologies and therapeutic endpoints. Further, the cause of the pathological condition different. For example, surgery, stasis, nephrotic syndrome, pregnancy or other medical conditions associated with thrombus formation. Septic shock is associated with gram-negative infections. Septic shock can also follow gram-positive bacterial, ricketsial, viral and fungal infections. In addition noninfectious insults such as trauma, haemorrhage and pancreatitis can cause SIRS. Therefore, each condition represents patentably distinct subject matter. Regarding Groups VII and VIII and (VI11 and IV-VI) are related as product and process of using. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP j 806.05(h)). In the instant case the antibody of Group VIII, and the ligands of Group VII can be used for affinity purification, in addition to the methods of preventing and/or treating recited. Further, a prior art search also requires a literature search. It is an undue burden for the examiner to search more than one invention.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 2-4 and 13-20 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1, 5-12 and 21 are under examination as they read on a method for preventing and/or treating the systemic inflammatory response syndrome with a partial inhibitor of factor VIII,

wherein the partial inhibitor is an antibody and the antibody that is produce by KRIX 1 or anti-fVIII C1 domain antibody.

5. Applicant's IDS, filed 3/17/03 and 4/16/02, is acknowledged, however, the references 8, 10 and 11 were crossed because they are duplicates of references 1, 6 and 7, respectively.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 5, 8 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The term "having a reactivity substantially identical to" recited in claim 5, line 5 is ambiguous and unclear and the metes and bounds of the claimed "having a reactivity substantially identical to" is not defined. It is well known in the art that every antiserum has a different specificity because the repertoire of antibodies produced by animal is somewhat different. Thus, it is unclear one skill in the art would be able to make an antibody "having a reactivity substantially identical to" of the antibody produced by KRIX 1 hybridoma.

B. Claim 8 is indefinite in reciting "preferably" because the narrow range within the broad range using the term "preferably" renders the claim indefinite.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 5-12 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the hybridoma KRIX 1 that produce factor VIII antibody in claims 5 and 11 is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the hybridoma, which produces this antibody, may satisfy first paragraph. See 37 CFR 1.801-1.809.

If the deposit has been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridoma has been deposited under the Budapest Treaty and that the hybridoma will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample *or for the enforceable life of the patent whichever is longer*. See 37 CFR 1.806. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

Further, the specification does not reasonably provide **enablement** a method for preventing and/or treating the systemic inflammatory response syndrome in a mammal by administering any "partial inhibitor of factor VIII" to the said mammal in claim 1, wherein the partial inhibitor of factor VIII is a monoclonal antibody from a cell line producing human monoclonal antibodies having a "reactivity substantially identical to" that of the human monoclonal antibodies obtained from the cell line KIX 1 in claims 5 and 11 . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Beside, the human monoclonal antibody secreted by KRIX 1 hybridoma and anti-fVIII C1 domain antibody, Applicant has not provided sufficient biochemical information that distinctly identifies such "partial inhibitor of factor VIII". It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Applicant has not enabled structurally related and unrelated of "partial inhibitor of factor VIII" which would be expected to have difference in their activities. There is insufficient direction or objective evidence as to how to make and to how to use any partial inhibitor of factor VIII for the number of possibilities associated with the myriad of direct and indirect effects associated with various inhibitors and, in turn, as to whether such a desired effect can be achieved or predicted, as encompassed by the claims. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the structure of the "inhibitors" and still provide or maintain the claimed activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

In vitro studies have not correlated well with in vivo clinical trial results in patients. Since the method of preventing and/or treating SIRS indices the inhibition of thrombus formation with the antibody that partially inactivate factor VIII but does not immunoreacts with the physiological function site of factor VIII can be species – and model-dependent, it is not clear that reliance on the in vitro results of an antibody that partially inhibits thrombin formation (page 26 under example 5 of the instant specification) accurately reflects the relative efficacy of the claimed *in vivo* partial inhibition in a mammal including a subject.

The exemplification is drawn to the reduction of thrombin formation by decreased levels of factor VIII in vivo using normal factor VIII concentrations or the corresponding factor VIII knockout strain injected with lipopolysaccharide from *E. coli* to assess the inflammatory trigger exemplified by increased IL-6 levels (see pages 26-27 under Example 6). One cannot extrapolate the teachings of the specification to the scope of the claims because the method claims are drawn to treating and/or preventing SIRS in mammal including human using partial inhibitors of factor VIII. The specification lacks empirical data on the in vivo efficacy of anti-factor VIII on mammal including human. It is noted that the specification does not provide exemplification or animal model to treat human patients at risk for suffering from SIRS neither does the specification provide clear solutions to the pathophysiological condition from the an animal model to human. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the human monoclonal antibody secreted from KRIX 1 hybridoma or anti-fVIII C1 domain as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed method of preventing and/or treating SIRS are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed method with a reasonable expectation of success.

The lack of any working examples is exacerbated because the invention is in a highly unpredictable art-prevention and/or treatment- and while the level of skill of in the art may be high, the state of the prior art is that it is in fact unknown and untested what are the underlying molecule and physiologic bases of the therapeutic effects of anti-factor VIII antibody in the prevention and/or treatment of SIRS. Inhibitor antibodies manifest themselves by neutralizing factor VIII activity and/or accelerating the clearance of factor VIII. Depleting factor VIII from the plasma would induce a bleeding state. Patients with antibodies against factor VIII usually present with spontaneous bleedings involving soft tissues, retropharyngeal or retroperitoneal speces, intracerebral or other types of serious hemorrhagic episodes.

Taylor *et al* (blood 89:4078-4084, 1997) utilize an animal model of *E .coli* infection using $F(ab')_2$ fragments of monoclonal antibody 7E3 were used to investigate the influence of this fibrinogen receptor-antagonist on microvascular changes . The baboons were infected with *E. coli* and treated with C4b-binding protein (C4bBP). While the treated group showed a positive effect on the survival rate, however, an extrapolation of these data to humans is impossible for several reasons. Such animal model would not work in human because the pathophysiology of the animal model and comparable human disorders in strikingly different and the co- treatment

of the baboons with the C4bBP in addition to the bacteria results in an artificial pathophysiological state which is never encountered in the treatment of human patients (see page 4083, 2nd col., in particular). Therefore, there is insufficient guidance in the specification as to how it can be assessed that treatment of SIRS in the humans was achieved after the administration of the partial inhibitor of fVIII antibody of the invention.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. Claims 1, 5-12 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of *in vitro* method of partially inhibit thrombin formation with anti-fVIII C1 domain antibody.

Applicant is not in possession of a method for preventing and/or treating the systemic inflammatory response syndrome in a mammal by administering any "partial inhibitor of factor VIII" to the said mammal in claim 1, wherein the partial inhibitor of factor VIII is a monoclonal antibody from a cell line producing human monoclonal antibodies having a "reactivity substantially identical to" that of the human monoclonal antibodies obtained from the cell line KIX 1 in claims 5 and 11.

Applicant has disclosed only anti-fVIII C1 domain antibody to partially inhibit thrombin formation in vitro; therefore, the skilled artisan cannot envision all the contemplated partial inhibitor of factor VIII possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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